

REMARKS

The examiner rejects claims 1 and 2 under 35 U.S.C 112 first paragraph stating that when R_2 is methylene the reactant is a hemiaminal which is unstable and will yield a Schiff base. The examiner has not provided any support for this statement. The attached page 11 of 22 from Review of Selected Topics in Organic Chemistry describes hemiaminals and shows a hemiaminal which is of a different structure than any compound of claim 1. In formula I of claim 1, R_2 is a bridge between the nitrogen atom and the hydroxy group. According to the selected Review of Selected Topics in Organic Chemistry, hemiaminals are formed by hydrating imines or by the addition of amine to a carbonyl group of a ketone or aldehyde. According to Grant & Hackh's Chemical Dictionary, a Schiff base is a condensation product of an aromatic amine and aliphatic aldehyde. Diethanolamine is known to possess sufficient stability to be a reactant and is not a ketone or an aldehyde and therefore, there is no basis for the examiner's rejection.

Therefore, in view of the above, it is respectfully requested that the rejection under 35 U.S.C 112 be withdrawn and that this application be allowed.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,



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GRANT & HACKH'S CHEMICAL DICTIONARY

[American, International, European and British Usage]

*Containing the Words Generally Used in Chemistry,
and Many of the Terms Used in the Related
Sciences of Physics, Medicine, Engineering,
Biology, Pharmacy, Astrophysics,
Agriculture, Mineralogy, etc.*

Based on Recent Scientific Literature

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- discrete energy states; *Raman effect*, where the scattered light results from a continuum of virtual energy states; *Compton effect*, where a quantum of high frequency (*X-rays*) dislodges an electron from the scattering substance. Cf. *luminescence*.
- scavenger** A purifying substance; as, metallic lithium which removes impurities from alloys.
- Schaffer's acid** $\text{HSO}_3 \cdot \text{C}_{10}\text{H}_6 \cdot \text{OH} = 224.2$. Armstrong's acid. β -Naphtholsulfonic acid, 2-hydroxynaphthalene-6-sulfonic acid; used in organic synthesis.
- schapbachite** $\text{PbS} \cdot \text{Ag}_2\text{S} \cdot \text{Bi}_2\text{S}_3$. A native sulfide.
- schappe** Silk waste.
- Schardinger dextrin** α -Dextrin.
- Scheele S.**; Carl Wilhelm (1742-1786) Swedish apothecary noted for his discovery of oxygen, chlorine, ammonia, manganese, and barium. S.'s green CuHASO_3 . An acid copper arsenite used as pigment.
- scheelite** CaWO_4 . A native calcium tungstate.
- scheelium** Tungsten (obsolete).
- scheererite** A mineral hydrocarbon, m. 45, b. 92.
- Scheibler S.**, Carl (1827-1899) German chemist noted for developments in the sugar industry. S.'s reagent A solution of phosphotungstic acid; yellow precipitate with sulfates of the alkaloids.
- Schick test** A test for susceptibility to diphtheria in which intracutaneous injection of toxin, from *Corynebacterium diphtheriae*, produces a local reaction.
- schieferspar** A flaky variety of calcite.
- Schiff S.**, Hugo (1834-1915) German organic chemist. S. bases* R-N:CHR. Condensation products of aromatic amines and aliphatic aldehydes forming azomethines substituted on the N atom: $\text{PhNH}_2 + \text{OCH} \cdot \text{Ph} = \text{PhN:CHPh} + \text{H}_2\text{O}$. S. reagent Thioacetic acid*. S. solution A solution of 0.2 g rosaniline and 15 mL sulfuric acid in 200 mL water; a test for aldehydes which restore the red color.
- schiller spar** Bronzite.
- schinus oil** An essential oil from the pepper tree, *Schinus molle* (Anacardiaceae), N. America, d. 0.850, containing phellandrene, pinene, and carvacrol.
- schist** A crystalline rock that can be split into scales or flakes.
- schistic** Not aschistic, q.v. (*aschistic process*).
- schistosomiasis** Bilharziasis. A helminth disease in tropical countries.
- Schizomycetes** *Schizophyta*, fission fungi, *bacteria*, q.v. Plant microorganisms of the chlorophyll-free, fungi class.
- Family 1: *Coccaceae*, round or spherical in shape.
- Genus I: *Streptococci*, beadlike chains.
- Genus II: *Micrococci*, grapelike clusters.
- Genus III: *Sarcina*, balelike packs.
- Genus IV: *Planococci*, like II but mobile.
- Genus V: *Planosarcina*, like III but mobile.
- Family 2: *Bacteriaceae*, cylindrical or rodlike in shape.
- Family 3: *Spirillaceae*, curved or S-like in shape.
- Schizophyta** *Schizomycetes*.
- schlempe** Vinasse.
- schlieren** Describing the region of changing refraction in an otherwise optically homogeneous medium, e.g., heat waves seen over a hot surface.
- Schlippe S.**, Carl Friedrich von (1789-1874) German-born Russian chemist. S.'s salt $\text{Na}_2\text{SbS}_4 \cdot 9\text{H}_2\text{O}$. Sodium tetrathioantimonate*.
- Schlotterbeck reaction** The synthesis of ketones from aldehydes: $\text{R} \cdot \text{CHO} + \text{CH}_2\text{N}_2 \rightarrow \text{R} \cdot \text{CO} \cdot \text{CH}_3 + \text{N}_2$. Cf. *Nierenstein reaction*.
- Schmidt test** A test for glue; white precipitate with a solution of ammonium molybdate.
- Schmoluchowski's equation** The average path length, in μm , of a particle in a dispersed system: $2.37 \sqrt{K} \cdot \text{RT} \cdot t / Lq$, where R = gas content, L = Avogadro constant, T = thermodynamic temperature, t = period of vibration of the particle, η = viscosity of the medium, r = radius of the particle.
- schneebergite** CaSbO_3 . A native antimonite.
- Schneider's furnace** A retort for the distillation of zinc from zinc-lead ores.
- Schoenbein, Christian Friedrich (1799-1868)** German chemist noted as discoverer of ozone and for work on catalysis.
- Schoenherr process** A nitrogen fixation method in which the air circulates spirally around a 6-meter electric arc.
- schötenite** $\text{K}_2\text{SO}_4 \cdot \text{MgSO}_4 \cdot 9\text{H}_2\text{O}$. A stassfurt salt.
- Schöllkopf's acid** (1) 1-Naphthol-4,8-disulfonic acid. (2) 1-Naphthylamine-4,8-disulfonic acid. (3) 1-Naphthylamine-8-sulfonic acid.
- schorl** Tourmaline.
- Schörlemmer, Carl (1834-1900)** German chemist, noted for his textbooks.
- schorlomite** A titanium garnet, q.v.
- Schöttgen S.**, Carl (1853-1910) German organic chemist noted for his organic synthesis methods. S. reaction Acylation in alkaline solution with benzoyl chloride.
- schou oil** A gelatinous product of the oxidation of soybean oil; an emulsifying agent in the margarine industry.
- schraufite** $\text{C}_{11}\text{H}_{16}\text{O}_2$. A fossil resin in Carpathian sandstone.
- schreibersite** $(\text{FeNiCo})_3\text{P}$. A mixed phosphide, in certain meteorites.
- schreiner** Reduction of the fiber interstices of a knitted fabric to give a tighter structure and higher density.
- Schrödinger S.**, Erwin (1887-1961) Austrian physicist, Nobel prize winner (1933); noted for his atomic concepts. S. atom Pulsating or fluctuating atom. The atom is regarded as a sphere of electricity which may vary in its density, but which may pulsate, with absorption or liberation of radiation. S. equation Wave equation. An equation, based on de Broglie's equation, in which ψ^2 determines the statistical charge density. In 3 dimensions it is: $\nabla^2\psi + (8\pi^2m/h^2)(E - U)\psi = 0$, where ∇^2 is the Laplace operator, ψ the wave function, E the total energy, U the potential energy, and m the mass of the particle. Cf. *Heisenberg principle*.
- schroekingerite** Dakerite.
- Schroeder's paradox** Polymers swell more in a liquid than in its vapor, owing to small temperature differences.
- Schrötter apparatus** Calimeter.
- Schultz number** The classification number of a dyestuff as given in "Farbstofftabellen," by Gustav Schultz. Cf. *Color Index*.
- Schulze's rule** The precipitating effect of an ion varies with its valency.
- Schumann rays** The extreme ultraviolet portion of the spectrum which affects a photographic plate. Cf. *ultraviolet*.
- Schütz-Borrisow rule** Enzyme activity; $x = tK\sqrt{c}$, where x is the amount of substance digested, t the reaction time, e.g., 24 hours, K a constant, and c the concentration of the enzyme.
- Schwarz** Trademark for a viscous synthetic fiber.
- schwartzite** A tetrahedrite containing mercury.
- Schweinfurt green** Cupric subacetate.
- Schweitzer S.**, Mathias E. (1818-1860) German chemist. S.'s reagent An ammoniacal solution of cupric hydroxide, which dissolves cellulose.
- schwellenwert** Liminal value, threshold value. The minimum quantity of electrolyte required to precipitate a colloidal solution.
- sciadopitene** $\text{C}_{20}\text{H}_{32} = 272.5$. A diterpene, m. 96, from the

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Review of Selected Topics in Organic Chemistry

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1 Atomic Connections

See chapter 1, sections 1.1, 1.2 and 1.5 of Bruice for more information on atomic orbitals.

1.1 Quantum Nature of Atoms

In the atmosphere of the Sun, there exists so much energy that atoms do not associate with each other. The nuclei of atoms do not even associate with electrons. This mixture of nuclei and electrons is called plasma. At the temperatures and pressures that exist on Earth (as opposed to the center of the Sun), atoms will associate with electrons to satisfy the mutual attraction between opposite charges. Electrons are very light particles and move at such a speed that they behave more like electromagnetic energy (wavelength) rather than particles (velocity and position). Nuclei, being much more massive than electrons, mostly behave like particles.

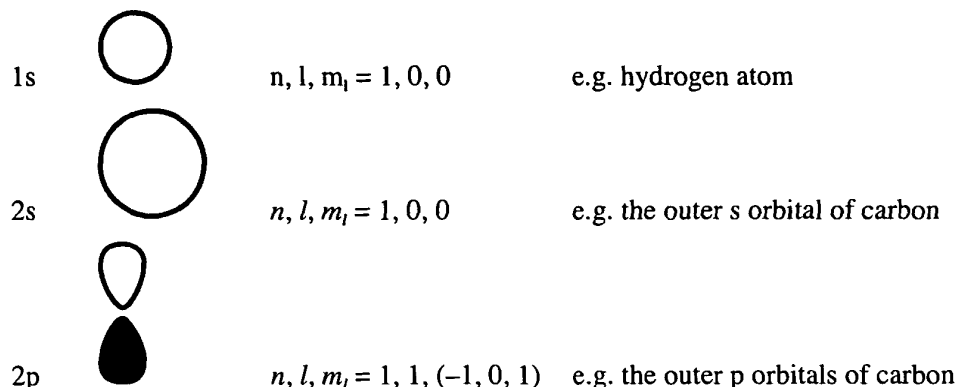
1.2 Atomic Orbitals

To satisfy the wavelengths of these electrons the electronic structure of atoms comes to involve the quantum energy levels and each electron can be described by the 4 quantum numbers. The first three quantum numbers describe each atomic orbital for the atoms and the last quantum number describes each of the two electrons that may occupy that orbital. These atoms (a nucleus with its associated electrons) can associate with other atoms in a variety of manners to satisfy mutual repulsions and attractions. Some of these associations are weak (e.g. Van der Waals forces, dipole interactions) and some are strong (e.g. covalent bonds).

Figure 1. Quantum numbers for describing electrons associated with an atom.

| | | |
|-------|---------------------------------|--------------------------------|
| n | principle quantum number | $n = 1, 2, 3, \dots$ |
| l | angular momentum quantum number | $l = 0, \dots, n-1$ |
| m_l | magnetic quantum number | $m_l = -l, \dots, 0, \dots, l$ |
| m_s | spin quantum number | $m_s = -1/2 \text{ or } +1/2$ |

Figure 2. Some example atomic orbitals.



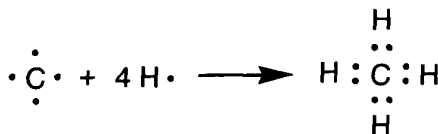
1.3 Covalent Bonds

See chapter 1, sections 1.3 and 1.4 of Bruice for more information on covalent bonds and Lewis structures.

Neutral carbon, hydrogen, oxygen and other similar atoms are in their most stable arrangement if they can share unpaired electrons with other atoms so that each atom can fill its valence shell. Hydrogen requires 2 electrons in its valence shell. Most other elements we will see prefer 8 electrons in their outer valence shell. Some elements, such as phosphorous and sulfur, are perfectly happy with 8 or 10 electrons in the outer valence shell.

Covalent bonds are the strong interactions between atoms that are sharing electrons to fill their mutual valence shells. An example is methane: A neutral carbon atom with 4 electrons in its outer valence shell can share electrons with 4 neutral hydrogen atoms with one electron each in their outer valence shells. The four electrons from the hydrogen atoms fill up the carbon valence shell to the most stable arrangement of 8 electrons. One electron from carbon is shared with each hydrogen atom and fills the hydrogen atom's valence shell to the preferred 2 electrons.

Figure 3. Lewis structure of methane.



1.4 Ionic Associations

See chapter 1, sections 1.3 and 1.4 of Bruice for more information on ionic bonds.

Some elements easily give up or accept an electron to become positively or negatively charged, respectively. Charged elements can form associations due to opposite charge attractions. An example is table salt, NaCl. Sodium easily gives up an electron and chlorine readily accepts an electron and so they are of opposite charge. Salt crystals form

from the ionic associations of Na^+ and Cl^- atoms. Electrons are NOT shared in ionic associations; the force between the atoms is due to opposite charge attraction.

1.5 Van der Waals Forces

See chapter 2, section 2.9 of Bruice for more information on Van der Waals interactions.

Ionic atoms can repel or attract each other depending on their mutual charges. Neutral atoms do not repel or attract each other; they are neutral in charge so there is no electromagnetic interaction over medium to large distances. However, when the distance between atoms is small there will be induced dipole interactions. The nucleus of one atom can be electrostatically attracted to the electrons of the other and vice-versa. This attraction is very weak and only becomes important when a neutral molecule of significant size is in Van der Waals contact with another similar molecule. The weak attractions between all the atoms may be enough to hold the two molecules near each other. This is why hexane can be a liquid. Hexane molecules have no attraction for each other than Van der Waals interactions, however these interactions are enough to hold a collection of these molecules together as a liquid below temperatures of 69 °C.

2 Molecular Structure

See chapter 1, section 1.6 of Bruice for more information on molecular orbitals and σ and π bonds.

2.1 Molecular Orbitals

It is important to realize that molecules are more than balls connected by sticks, they are nuclei of atoms positioned in such a way that a stable electronic structure can form to allow for electron sharing in covalent bonds and the existence of stable non-bonded electron pairs. In a given molecule the atoms and non-bonded electron pairs will arrange themselves to be as far apart as possible while maintaining a distance such that electron pairing can occur. This idea that atoms will position themselves thus is called the valence shell electron repulsion theory (VSEPR). The atomic orbitals of the individual atoms that are sharing electrons will combine into molecular orbitals that define the electron configuration the bond between the two atoms involved.

2.1.1 σ Bonds

When two orbitals overlap to form a single bond, they will overlap in the most stable form possible. This is almost always to orient them along an axis of infinite rotation (you can rotate the orbital any amount, large or small, and you wouldn't know that you had done so). The combined atomic orbital will form a new molecular orbital. Two orbitals CANNOT occupy the same space at the same time. But they can combine into a new pair of molecular orbitals and will do so if the new molecular orbital is lower in energy than the original two atomic orbitals. This new molecular orbital will also have infinite rotational symmetry and is designated a σ bond because of that symmetry.

2.1.2 π Bonds

Often two atoms joined by a σ bond will have p-orbitals available for overlap to form a second or a third bond between the atoms. p-Orbitals have two-fold symmetry (they can be rotated 180° and you wouldn't know it) and the molecular orbital formed by their overlap will also have two-fold symmetry and is designated a π bond because of that symmetry.

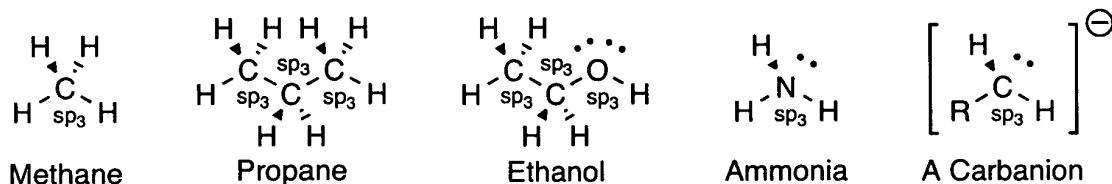
2.2 Hybrid Orbitals

See chapter 1, section 1.7, 1.8, 1.9 and 1.10 of Bruice for more information on hybrid atomic orbitals and the molecular orbital structure of molecules.

2.2.1 sp_3

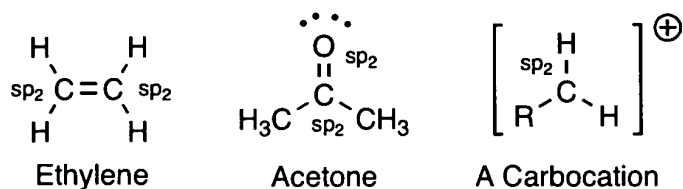
In order to explain the σ bond system of atoms it is convenient to invoke fictional hybrid orbitals. Methane has 4 hydrogen atoms bonded to a central carbon atom; they are spaced in a tetrahedral arrangement 104° apart in agreement with the VSEPR theory. We need 4 carbon atomic orbitals to overlap individually with 4 hydrogen atomic orbital to construct the 4 single bonds of methane. Carbon has a 2s and three 2p orbitals in its valence shell. These four orbitals could each be overlapped with a 1s orbital from each hydrogen atom but that would not explain the geometry of methane. Each p-orbital is 90° from the other, not 104° as is observed in methane. In reality, the hydrogen atoms spread out around the carbon to maximize the distance between them and each will overlap with a part of each of the 2s and 3 2p atomic orbitals of the carbon atom depending on how close each hydrogen atom is to each carbon atomic orbital. It is as if the 2s and 3 2p atomic orbitals are combined to form 4 new sp_3 atomic orbitals spaced 104° from each other. Basically, when we say a carbon is tetrahedral we also can say is a sp_3 carbon.

Figure 4. Tetrahedral sp_3 hybridized carbon atoms.



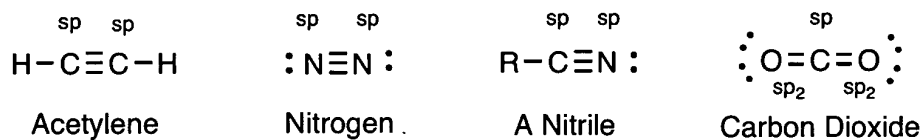
2.2.2 sp_2

Similarly, a carbon with three substituents will adopt a trigonal planar arrangement and three atomic orbitals are needed to establish the 3 hybrid atomic orbitals that define the σ bond system. The 2s and 2 2p atomic orbitals of the carbon atom will be mathematically combined to create the three fictional sp_2 orbitals. There will be a spare 2p atomic orbital left over orthogonal to the plane of the 3 sp_2 orbitals. It can overlap with another p orbital of an adjacent atom to create a π bond. sp_2 hybridized carbons often are observed with two single (σ bonds) and a double bond (σ bond + π bond). When a carbon is trigonal planar we can say it is a sp_2 carbon.

Figure 5. Trigonal planar sp_2 hybridized carbon atoms.

2.2.3 SP

Also, sp hybridized carbons are invoked to describe the σ bond system of a carbon with two substituents. According to VSEPR theory, the two substituents will be on opposite sides of the carbon atom to form a linear system. Two sp hybrid atomic orbitals are formed from the mathematical combination of a $2s$ and a $2p$ atomic orbital of a carbon atom. This leaves two non-hybridized $2p$ atomic orbitals on the carbon atom that can overlap with p orbitals in the adjacent atoms and form two π bonds. This may result in a triple bond (σ bond + 2 π bonds) to one substituent and a single bond to the other or double bonds (σ bond + π bond) to both substituents. When a carbon is part of a linear system we can say that it is a sp carbon.

Figure 6. Linear sp hybridized carbon atoms.

3 Oxidation and Reduction

In organic molecules, when we add or remove substituents, we may often add or remove electrons with these groups. Changing the number of electrons in a molecule or part of a molecule will alter the oxidation level of that molecule or group. Oxidation/reduction as it relates to carbon groups is often described in terms of adding or removing hydrogen atoms. It is more correct to think of adding or removing electrons. Remember, the hydrogen atoms have electrons. Removing a pair of hydrogen atoms will also remove a pair of electrons.

3.1 Oxidation States

The oxidation state of a carbon center can be described by adding up the electrons it controls. Substituents with the same electronegativity as carbon (like another carbon) do not result in a carbon owning any more electrons and so count as "0" in calculating the oxidation state. Substituents that are less electronegative than carbon, such as hydrogen, result in the carbon owning an extra electron and so count as "-1" (electrons are negative). Substituents that are more electronegative than carbon, like oxygen, nitrogen or halogens, will result in the carbon owning one less electron per bond to the substituent and so count as "+1".

For example:

Methane: 4 hydrogen substituents ($4 \times (-1) = -4$), oxidation state = -4

Propane 1-carbon (at end): 3 hydrogen substituents ($3 \times (-1) = -3$), 1 carbon substituent (0), oxidation state = -3

Propane 2-carbon (centre carbon): 2 hydrogen substituents ($2 \times (-1) = -2$), 2 carbon substituents (2×0), oxidation state = -2

Acetylene carbon: 2 hydrogen substituents ($2 \times (-1) = -2$), 2 bonds to a carbon substituent (2×0), oxidation state = -2

Acetone carbon (a ketone): 2 carbon substituents (2×0), 2 bonds to oxygen substituent ($2 \times (+1) = +2$), oxidation state = $+2$

Carbon dioxide: 2 bonds each to 2 oxygen groups ($2 \times 2 \times (+1) = +4$), oxidation state = $+4$

Adding electrons to a carbon (moving toward a more negative oxidation state) is reduction (adding electrons is often analogous to adding hydrogen atoms). Remember that the electrons came from somewhere so another molecule or group of a molecule must donate those electrons and end up with fewer electrons. When a molecule gives up electrons it is being oxidized. We will see more of oxidation and reduction in functional group transformations.

4 Functional Groups

Your basic organic molecule might be a saturated carbon chain like propane. Such fully reduced carbon chains are difficult to alter chemically. In biological molecules we will have substituents on the carbon chains that impart functional chemistry and can be altered by chemical processes to produce energy or operate biochemical machinery. These functional groups are generally easier to alter than non-functionalized carbon chains and act as "handles" where most biological chemical transformations can take place. Having said that there are numerous cases where non-functionalized aliphatic carbon chains are altered by biological systems, a feat that is difficult even in our own chemical laboratories.

For more information on the nomenclature and structure of functional groups see the following sections of Bruice: 2.1 (alkyl groups), 2.2 (alkanes), 2.3 (cycloalkanes), 2.5 (ethers), 2.6 (alcohols), 2.7 (amines).

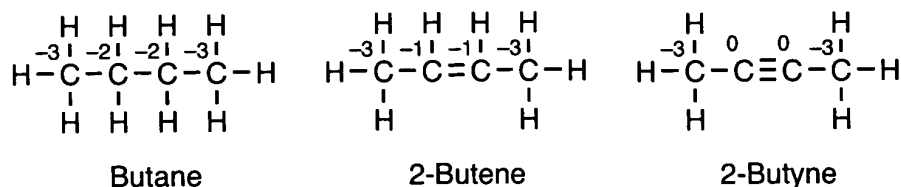
4.1 Unsaturated bonds

A saturated carbon chain has only single bonds between carbons and hydrogen atoms on each carbon so that there is a total of 4 bonds (all sp_3 carbons). If we dehydrogenate the carbon chain we remove 2 hydrogen atoms, usually as a hydride (a proton and 2 electrons) and a proton. We now have a double bond and each carbon has a higher oxidation state (from -2 to -1 for each carbon for carbons internal to the chain). Compounds that contain a carbon-carbon double bond are called **alkenes**.

See chapter 3, section 3.1, 3.2, 3.3 and 3.4 of Bruice for more information on alkenes

Further dehydrogenation would result in a triple bond and the carbons now have an oxidation state of 0 (assuming the triple bond is internal to the chain). Such compounds are called **alkynes**.

Figure 7. Saturated and unsaturated hydrocarbons with carbon oxidation states indicated.

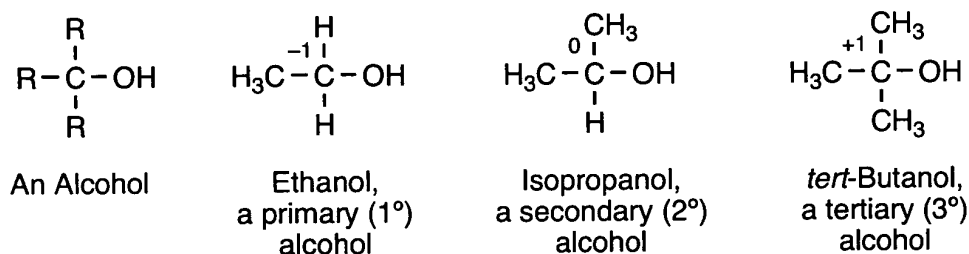


4.2 Oxygen groups

4.2.1 Alcohols

Perhaps the most familiar functional group is the **alcohol** group, a hydroxyl connected to a carbon by a single bond (carbon oxidation state is noted below for each type of alcohol)

Figure 8. Some alcohols with carbon oxidation states indicated.

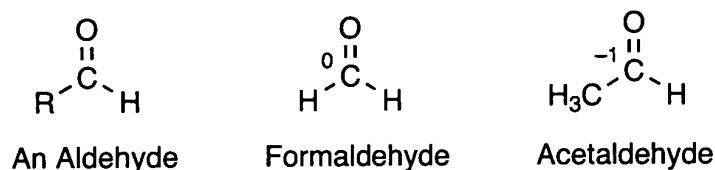


See chapter 2, sections 2.6 and 2.8 of Bruice for more information on alcohols

4.2.2 Aldehydes

Dehydrogenating a primary alcohol will give an **aldehyde**, a carbon group with two bonds to an oxygen atom and a single bond to a hydrogen atom (carbon oxidation state is generally -1)

Figure 9. Some aldehydes with carbon oxidation states indicated.

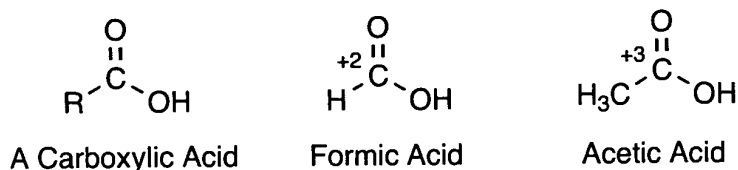


See chapter 18, sections 18.1 and 18.2 of Bruice for more information on aldehydes.

4.2.3 Carboxylic Acids

A carbon with a double bond to an oxygen atom and a single bond to a hydroxyl group is a **carboxylic acid** (carbon oxidation state is generally +3).

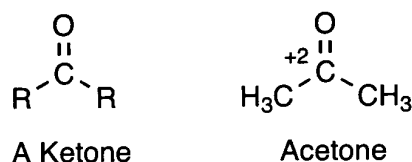
Figure 10. Some carboxylic acids with carbon oxidation states indicated.



4.2.4 Ketones

Dehydrogenating a secondary alcohol will give a **ketone**, a carbon with 2 bonds to an oxygen atom and no hydrogen groups (carbon oxidation state is +2).

Figure 11. Some ketones with carbon oxidation states indicated.

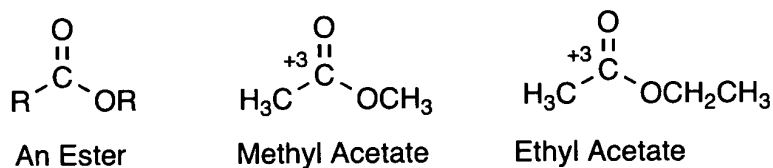


See chapter 17, sections 17.1 and 17.2 of Bruice for more information on aldehydes and ketones

Other important oxygen groups found in biological molecules are listed below with the oxidation state of the carbon indicated.

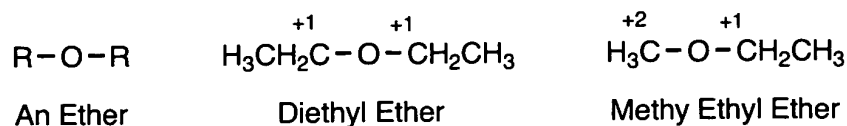
4.2.5 Esters:

Figure 12. Some esters with carbon oxidation states indicated.



4.2.6 Ethers:

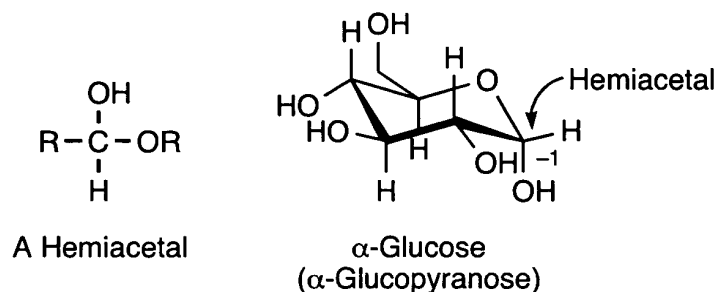
Figure 13. Some ethers with carbon oxidation states indicated.



4.2.7 Hemiacetals

The result of an alcohol oxygen atom attacking the carbon atom of an aldehyde group. Reaction is easily reversed to give the original alcohol and aldehyde.

Figure 14. A hemiacetal with the hemiacetal carbon oxidation state indicated.

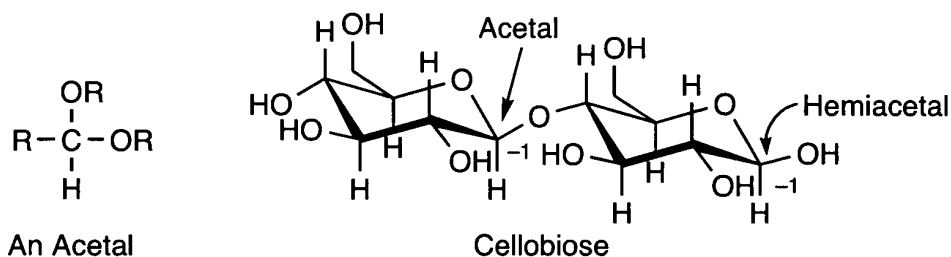


See chapter 17, sections 17.X of Bruice for more information on hemiacetals and hemiketals

4.2.8 Acetals

Can be thought of as a hemiacetal where the free hydroxyl group has been alkylated with a carbon group. Acetals have a carbon group on the hydroxyl (this is an ether linkage) and hemiacetals have a hydrogen atom on the hydroxyl (think of H is for "hemi").

Figure 15. An acetal with the acetal carbon oxidation state indicated.



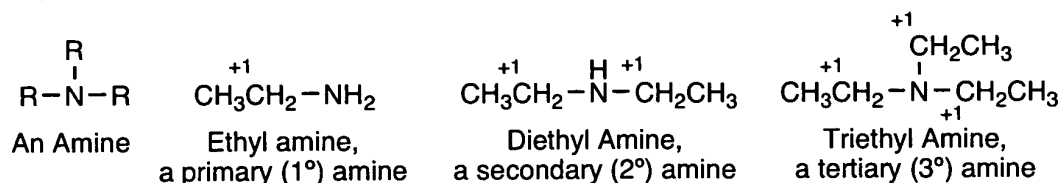
See chapter 17, sections 17.8 of Bruice for more information on acetals and ketals

4.3 Nitrogen Groups

4.3.1 Amines

A nitrogen atom with single bonds to carbons or hydrogen atoms is an **amine**. As in the case of alcohols, the number of carbon substituents determines if the amine is primary, secondary or tertiary.

Figure 16. Amines with the carbon oxidation states indicated.



See chapter 2, sections 2.7 and 2.8 of Bruice for more information on amines.

4.3.2 Imines

If we dehydrogenate a primary or secondary amine we can get an **imine** or Schiff base, which is a nitrogen with a double bond to a carbon.

Figure 17. Imines with carbon oxidation states indicated.

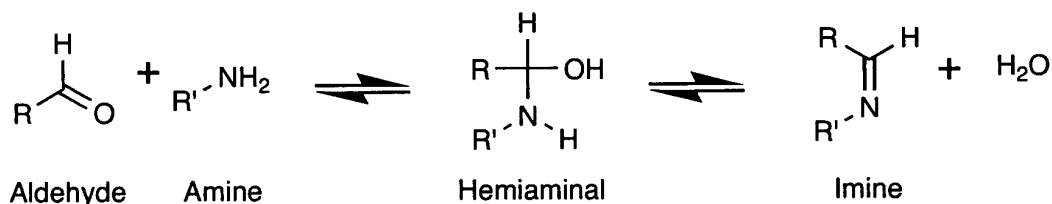


See chapter 17, section 17.7 of Bruice for more information on imines.

Imines can be easily hydrated to give a **hemiaminal**. Hemiaminals can be easily dehydrated to give imines.

A hemiaminal is also easily formed from the addition of an amine to a carbonyl group of a ketone or aldehyde. So we can see that addition of an amine to an aldehyde followed by dehydration (both easy, reversible reactions in water) can lead to the formation of an imine. **THIS IS ONE OF THE MOST IMPORTANT REACTIONS IN BIOCHEMISTRY!** You will see this reaction many, many times in Chemistry 352.

Figure 18. Formation of hemiaminals and imines from an aldehyde or group and an amine group.



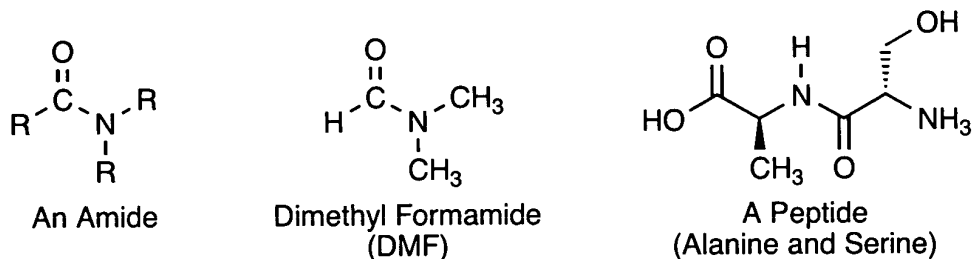
See chapter 17, section 17.X of Bruice for more information on imine formation from aldehydes and ketones.

4.3.3 Amides

A carbon atom with a double bond to an oxygen atom and a single bond to an amine is an **amide**. The carbon atom and oxygen atoms are sp_2 hybridized, as expected. The nitrogen might be expected to be sp_3 hybridized as it has three groups attached plus a non-bonded electron pair for a total of 4 groups (which would prefer to be tetrahedral according to VSEPR theory). However, it is more stable to have the lone pair in a p-

orbital parallel to the p-orbitals of the carbon and oxygen so that they can be stabilized by overlapping with the p-orbitals in the π -bond between the C and the O. Because the p-orbital is overlapping with the π -bond it is not available to contribute to the hybrid atomic orbitals and the result is a sp_2 hybridized nitrogen atom and the C-atom, the O-atom and the N-atom and its substituents will all be in the same plane.

Figure 19. Amides.



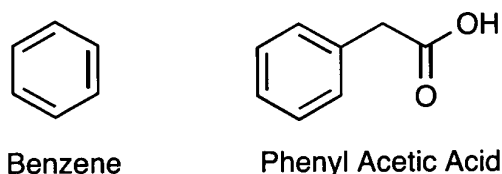
We will see that amide groups are often called **peptide** bonds or peptide linkages when they occur between two amino acids.

See **chapter 16, section 16.1 of Bruice** for more information on amides.

4.4 Aromatic Compounds

Cyclic conjugated compounds may be aromatic if the π -bond system in the ring contains 2, 6 or 10 electrons ($2n + 2$ rule, $n = 0, 1, 2, \dots$). **Benzene** is the most famous aromatic system. Benzene rings are often called **phenyl rings** when they are part of another molecule. All atoms in an aromatic system are sp_2 hybridized and the system is planar.

Figure 20. Examples of compounds with phenyl rings.

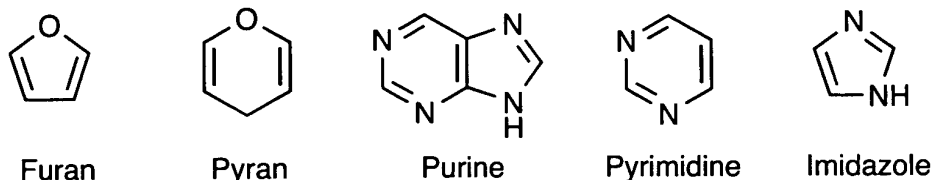


See **chapter 14, section 14.1 and 14.2 of Bruice** for more information on aromatic compounds.

4.5 Heterocycles

Some important heterocyclic compounds are present in one form or another in biochemistry. Cyclic forms of sugars can be described as having a hydrated furan or pyran skeleton. Nucleotide bases like uridine and cytidine are derivatives of pyrimidine and guanine and adenine are derivatives of purine.

Figure 21. Examples of heterocyclic compounds.



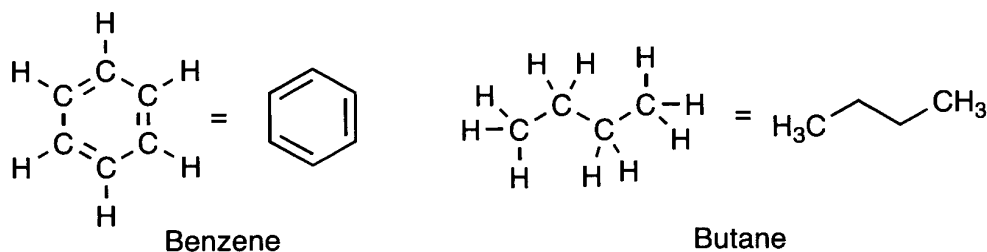
See chapter 14, section 14.3 of Bruice for more information on heterocyclic compounds.

5 Molecular Structures II

5.1 Structural Representations

Usually, I will present molecules using stick notation for the carbon skeleton and any non-carbon atoms other than hydrogen. Hydrogen atoms will only be shown if they are connected to non-carbon atoms or are necessary to make a point. Carbon atoms should be assumed to have the correct number of hydrogen atoms.

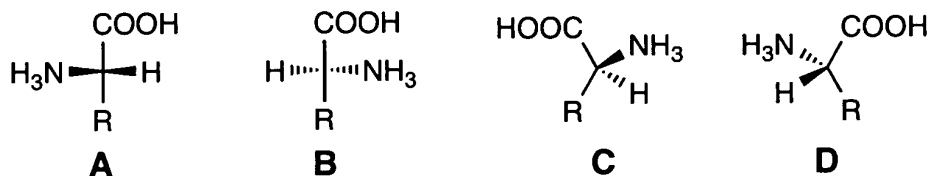
Figure 22. Graphical structural representations of organic molecules.



5.2 Stereochemistry

Organic molecules that contain one or more sp_3 (tetrahedral) carbons will have a three dimensional structure. Three-dimensional structure around a carbon can be indicated by “wedges” that indicate if a substituent is in front of the carbon (solid wedge) or behind (dotted wedge) relative to the observer.

Figure 23. 3-Dimensional graphical structural representations of an organic molecule.



Structure A, above, obviously has the amine group and the hydrogen atom in front of the carbon atom. Since carbon is tetrahedral with 4 groups (sp_3 hybridized), the carboxylic acid group and the substituent (R group can be any group) are behind. Structure B is the same compound rotated 180° and we are choosing to indicate the amine group and the

hydrogen atom behind the carbon atom and the carboxylic acid group and the substituent (R group can be any group) are therefore in front. Structures C and D are also the same molecule as A.

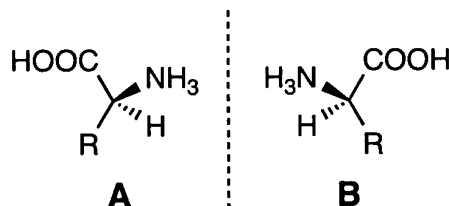
5.3 Chiral Molecules

The above structure A is obviously an amino acid (**Bruice, sections 21.1 and 21.2**) and like most amino acids it has 4 different substituents around a carbon atom. This carbon atom is thus asymmetrical – there is no symmetry operation that one can perform (e.g.: rotation; mirror reflection; improper rotation) that would result in a redundant structure (**Bruice, sections 4.3, 4.4 and 4.5**). A carbon atom that is asymmetrically substituted is called a chiral carbon or a chiral centre. A molecule with one or more chiral carbon atoms is a chiral molecule.

As a result of containing an asymmetric carbon, a chiral molecule is also asymmetric. Chiral molecules have no symmetry operations that would result in a redundant structure. Another way to say this is to state that there is no way to superimpose the mirror image of a chiral molecule on top of the original molecule.

There are two possible configurations for a chiral center; each is a mirror image of the other. These two possibilities are termed **enantiomers**. Structure A and B below may look identical to structures C and D above but look closely. Structure B is the mirror image of structure A. It cannot be rotated to be superimposable on A.

Figure 24. Two enantiomers of an amino acid.



See chapter 4 of Bruice and chapter 3, section 3.1 of Stryer for more on chiral compounds

6 Acids and Bases

See chapter 1.16, 1.17, 1.18 and 1.19 (1.19 resonance stabilization) of Bruice for more information on acids and bases. Most freshman and high school chemistry textbooks contain detailed discussions on acid/base equilibria.

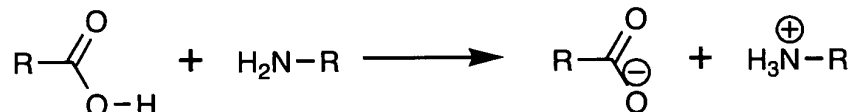
6.1 Definitions

The Brønsted definition of acids and bases is that acids are compounds that can donate a proton to a base and a base is a compound that can accept a proton from an acid. This definition of acids and bases is adequate for the understanding of biochemistry.

An acid cannot be an acid unless there is a base onto which to donate the proton. Let us consider a carboxylic acid group in a molecule and an amine group in another molecule.

If they encounter each other the proton will likely be donated to the amine as amine groups have a high affinity for protons and carboxylic acids only have a moderate affinity for protons.

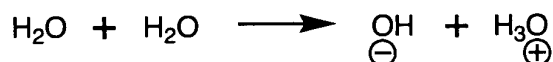
Figure 25. Exchange of an acid proton between a carboxylic acid and a basic amine.



6.2 Water

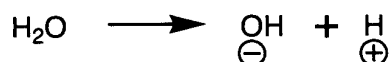
Water is both an acid and a base. H_2O can donate a proton to another H_2O to give a hydroxide ion (OH^-) and a hydronium ion (H_3O^+). In pure water at 25 °C the concentration of hydroxide and hydronium is 10^{-7} moles/L.

Figure 26. Acid equilibrium of water.



For the conventions of biochemistry, we will almost always write the dissociation of water as H_2O “splitting” into hydroxide and free proton. Free proton will NEVER exist in water. Protons will only ever be transferred from an acid to a base in water (and water may be the acid, the base, or in this case both). This convention is used because of historical reasons (before the hydronium ion was thought to exist).

Figure 27. Acid dissociation of water.



The equilibrium constant for this equilibrium is $10^{-15.7}$.

$$K_{eq} = \frac{[\text{OH}^-] \cdot [\text{H}^+]}{[\text{H}_2\text{O}]}$$

$$K_{eq} = \frac{10^{-7} \text{ M} \cdot 10^{-7} \text{ M}}{55.6 \text{ M}} = 10^{-15.7} \text{ M}$$

eq. 1

Note: The concentration of water in pure water is $(1000 \text{ g/L}) / (18 \text{ g/mole}) = 55.6 \text{ mole/L}$.

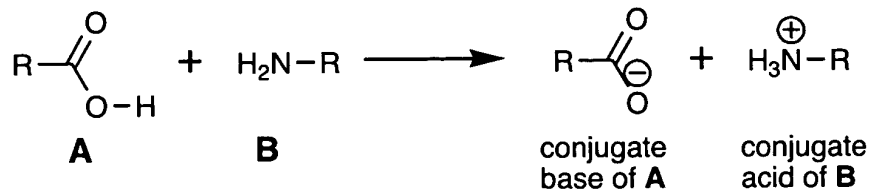
Other acids dissolved in water can donate their proton onto water, which would be the base. Water, acting as an acid, can donate a proton to a base.

6.3 Conjugate Acids and Bases

Anything that has a proton that can be donated can be an acid, anything that can accept a proton can be a base. When an acid donates its proton it is now a molecule that can

accept a proton back, so it is now a base. The base that results when a proton is removed from an acid is the conjugate base of that acid. The acid that results when a base accepts a proton is the conjugate acid of that base.

Figure 28. Conjugate acid and base.



6.4 Strong Acids and Bases

Some acids will dissociate completely in water. Hydrochloric acid (HCl) is an example. HCl will donate its proton to water and the concentration of hydronium ion will be the same as the concentration of HCl added. This is a strong acid. Any acid that dissociates completely in water is a strong acid. The concentration of hydronium can be assumed to be the concentration of acid added (unless there is another base present as well).

Some basic compounds will accept as much proton from water as there is base added resulting in a hydroxide ion concentration equal to the concentration of base added. These are strong bases. A good example is sodium hydroxide (NaOH), which dissociates completely to sodium ion and hydroxide ion in water.

6.5 pH

If a solution of 10 millimolar (mM) of hydrochloric acid is created, the concentration of acid proton (hydronium ion in water) will be also 10 mM as HCl completely dissociates in water. So the concentration of acid is 0.01 M or 10^{-2} M. To simplify description of acid proton concentration in water, we invoke the p function.

$p(x)$ is $-\log x$.

So $p(10^{-2})$ is $-\log(10^{-2})$ which is equal to 2.

$p[\text{H}]$ is written as pH . The $-\log$ of acid proton concentration is pH . From pH we can quickly know the concentration of acid proton (hydronium ion) and the concentration of hydroxide ion. Obviously, if the pH is 4 then the concentration of acid proton is 10^{-4} M. We also know the concentration of hydroxide ion because we know the acid dissociation constant for the dissociation of water to be $10^{-15.7}$.

For the dissociation of water we have the following reaction equation:



The acid dissociation constant, K_a , is given by the equilibrium equation:

$$K_a = \frac{[OH^-] \cdot [H^+]}{[H_2O]} \quad eq. 3$$

The concentration of water in dilute solutions does not change significantly with changes in pH. So $[H_2O]$ can be treated as a constant and combined with the acid dissociation constant, K_a , to create a new term called K_w .

$$K_w = K_a \cdot [H_2O] = [OH^-] \cdot [H^+] \quad eq. 4$$

K_w is the equilibrium constant for the dissociation of water multiplied by the concentration of water, which is considered to be constant. We will use the concentration of water in pure water, 55.6 M.

$$K_w = 10^{-15.7} M^{-1} \cdot 55.6 M = 10^{-14} \quad eq. 5$$

So

$$K_w = 10^{-14} = [OH^-] \cdot [H^+] \quad eq. 6$$

Applying the p function we get

$$pK_w = 14 = pOH + pH \quad eq. 7$$

So if the pH is 2 then the pOH must be 12 so $[OH^-] = 10^{-12}$. Obviously, the lower the pH value, the more acidic the water and the higher the pH value, the more basic the water.

6.6 Weak Acids and Bases

Strong acids dissociate completely (this is a simplified view) and there is no equilibrium between the acid and the water onto which it is transferring the proton. A weak acid is an acid that is not strong enough to push all of its acid protons onto water molecules but establishes an equilibrium with water in which it is only partially dissociated.

Let us use acetic acid (AcOH) as an example. In water, AcOH will be in acid equilibrium with water...



The equilibrium constant is given by

$$K_{eq} = \frac{[AcO^-] \cdot [H_3O^+]}{[AcOH] \cdot [H_2O]} \quad eq. 9$$

As before, in dilute solution the concentration of water is considered to be constant and can be ignored in the equilibrium equation, which can be rewritten as...



This equilibrium is the acid equilibrium (ignoring water). We use a new equilibrium constant to describe the above equilibrium; this is the acid dissociation constant, K_a . As in the case of K_w , K_a is the equilibrium constant multiplied by the concentration of water, which is constant.

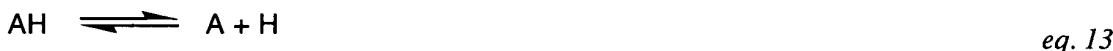
$$K_a = K_{eq} \cdot [\text{H}_2\text{O}] \quad \text{eq. 11}$$

So substituting eq. 9 into eq. 11 (remember, $[\text{H}^+]$ and $[\text{H}_3\text{O}^+]$ are the same thing) gives

$$K_a = \frac{[\text{AcO}^{\ominus}] \cdot [\text{H}^+]}{[\text{AcOH}]} \quad \text{eq. 12}$$

which is the equilibrium constant equation for equation 10.

For a general equation we can say that an acid (AH) dissociates to its conjugate base (A) and an acid proton (H) as outlined in eq. 13 (charges ignored for simplicity).



$$K_a = \frac{[\text{A}] \cdot [\text{H}]}{[\text{AH}]} \quad \text{eq. 14}$$

The larger the K_a value, the stronger the acid. We can simplify comparisons of K_a values by applying the p function. The acid dissociation constants for acids are usually presented as a pK_a value. We can apply the p function to eq. 14 to get the famous Hendersson-Hasselbach equation.

$$pK_a = pH - \log \frac{[\text{A}]}{[\text{AH}]} \quad \text{eq. 15}$$

Inspection of the HH equation reveals that if one arranges the pH of a solution of acid to be the same value as the pK_a , then half of the acid will be dissociated. A lower pK_a value indicates a stronger acid (more acid proton concentration needed to ensure 50% is protonated).

We can use pK_a values to discuss bases as well. The pK_a is the p function of the acid dissociation constant for the conjugate acid of the base. So we start with the protonated base and write the reaction equation for dissociation of the protonated base (conjugate acid of the base)



The larger the pK_a value, the stronger the base. We would expect that the acid dissociation constant, K_a , for the conjugate acid of a base would be small (basic compounds hold onto protons more strongly than acidic compounds) and so pK_a values for bases would be larger than for acids.

Remember, pK_a values represent how easily a protonated compound donates the proton to water (the acid is in equilibrium with water, which is the base in this equilibrium). Low values indicate a compound that readily donates protons to water. High values indicate a compound that will not easily donate protons to water.

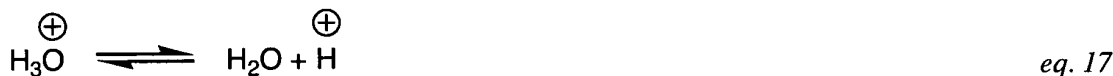
6.7 Review.

pK_a values, as used in biochemistry (and most chemical fields) refer to acid equilibrium in water. A protonated acid donates a proton to water to create the deprotonated conjugate base of the acid and a hydronium ion (recall eq. 8 for an example). The acid equilibrium contains a term for the concentration of water (recall eq. 9). In the case of dilute solutions we can say that the concentration of water is a constant and ignore it in the acid dissociation equation (recall eq. 10). The acid dissociation equation represents the acid molecule giving up its proton in a water molecule but we do not have water in the equation because its concentration does not change. The acid dissociation constant equation, eq. 12, is eq. 9 rearranged so that K_{eq} and $[H_2O]$ are combined to create the new acid dissociation constant, K_a (recall eq. 11).

6.8 pK_a of Water and Hydronium Ion

Hydronium ion is the strongest acid that can exist in significant concentrations in water. Acids stronger than hydronium will donate most of their protons to water to make hydronium ion in the same concentration as acid originally added. Hydronium ion is an acid (it has a proton it can donate to a base) and can donate a proton to a water molecule (the water is the base in this case).

The acid dissociation for hydronium ion is represented by...



And the acid dissociation constant equation is

$$K_a = \frac{[H_2O] \cdot [H^+]}{[H_3O^+]} \quad eq. 18$$

The K_a for hydronium ion is measured to be $10^{1.7}$ (at 25 °C). The large value indicates that it is a strong acid. The pK_a is -1.7 . The low value of the pK_a indicates that it is a strong acid.

Water can act as an acid and donate a proton to another water giving hydronium ion and hydroxide ion. This is the acid dissociation of water as discussed above (see eq. 2 and 3).



$$K_a = \frac{[OH^-] \cdot [H^+]}{[H_2O]} \quad eq. 3$$

The K_a for water is measured to be $10^{-15.7}$ (at 25 °C). The large value indicates that it is a very, very weak acid (The pK_a is 15.7). The high value of the pK_a indicates that it is a very, very weak acid. Conversely, the conjugate base of water, hydroxide ion, is a strong base. Hydroxide ion is the strongest base that can exist in water at a significant concentration. Stronger bases (bases whose conjugate acid has a larger pK_a value) will accept the protons from water to make as much hydroxide ion as base originally added.

6.9 pK_a Values of Weak Acids and Bases

Acids with a pK_a value of less than -1.7 are considered to be strong acids. If the conjugate acid of a base has a pK_a value greater than 15.7 it is considered to be a strong base. Weak acids and bases have pK_a values between these two extremes.

Table 1. pK_a values for selected acids and bases.

| Acid | pK_a |
|--------------|--------|
| HI | -10 |
| HCl | -7 |
| H_3O^+ | -1.7 |
| H_3PO_4 | 2.1 |
| CH_3COOH | 4.8 |
| $H_2PO_4^-$ | 7.2 |
| NH_4^+ | 9.4 |
| $CH_3NH_3^+$ | 10.7 |
| HPO_4^- | 12.3 |
| CH_3OH | 15.5 |
| H_2O | 15.7 |
| NH_3 | 36 |
| CH_3NH_2 | 40 |
| CH_4 | 50 |

We can use the famous Hendersson-Hasselbach equation (eq. 15) to calculate the percent of an acid (or base) that is in its acidic form (protonated) and its basic form (deprotonated).

Example 1. If we have a cell whose internal pH is measured to be 6.5, what is the percent of methylamine in its basic form in the cell?

The pK_a of methylamine is known to be 10.7 (see Table 1). We know the pH and we need to know the $[A]/[AH]$ ratio to calculate the percentage of methylamine in its basic form (this would be the conjugate base, A, of the acid, AH, in the HH equation)

So lets put in the values we know...

$$pK_a = pH - \log \frac{[A]}{[AH]} \quad \text{eq. 15}$$

$$10.7 = 6.5 - \log \frac{[A]}{[HA]}$$

$$-4.2 = \log \frac{[A]}{[HA]}$$

$$\frac{[A]}{[HA]} = 10^{-4.2} = 6.3 \times 10^{-5}$$

We can convert the $[A]/[HA]$ ratio to %A using the formula for converting a fraction to a percent. If the ratio is a value, x , the percent of the numerator is given by eq. 19

$$\% \text{numerator} = 100\% \cdot \left(\frac{x}{1+x} \right) \quad \text{eq. 19}$$

and the percent of the denominator is given by eq. 20.

$$\% \text{denominator} = 100\% \cdot \left(\frac{1}{1+x} \right) \quad \text{eq. 20}$$

So the % of the A form (the basic form) is 0.0063%. Obviously almost all of the methylamine is in its acidic form (99.994%) at that pH value.

Example 2. What if the pH of a solution of methylamine is arranged to be 10.7? What is the percent in its basic form under that condition?

Note that in this case the pH value is identical to the pK_a of the protonated methylamine. Lets do the math...

$$pK_a = pH - \log \frac{[A]}{[AH]} \quad \text{eq. 15}$$

$$10.7 = 10.7 - \log \frac{[A]}{[HA]} \quad \therefore 0 = \log \frac{[A]}{[HA]} \quad \therefore \frac{[A]}{[HA]} = 10^0 = 1$$

If the $[A]/[HA]$ ratio is 1 then we obviously have 50% in the basic form. Observe that when the pH of a solution is the same as the pK_a of an acid, the acid will be 50% deprotonated. As you can see in table 2

Table 2. Percent deprotonation for protonated methylamine ($pK_a = 10.7$) in water at various pH values.

| pH | Deprotonated |
|------|--------------|
| 7.7 | 0.10% |
| 8.7 | 1.0% |
| 9.7 | 9.1% |
| 10.7 | 50.0% |
| 11.7 | 90.9% |
| 12.7 | 99.0% |
| 13.7 | 99.9% |

Note the trends. When we are at a more basic pH value than the pK_a of the acid we have mostly the basic, deprotonated form (conjugate base of the acid). When we are at a more acidic pH value than the pK_a of the acid we have mostly the acidic, protonated form.

7 Other Topics of Interest

7.1 Dipole Moments.

See chapter 1, section 1.15 of Bruice for more information on dipole moments

7.2 Sugar Structure

See chapter 2 of Bruice for more information of sugar structure. Specifically, see sections 2.10, 2.11, 2.12, 2.13, 2.14, and 2.15 for more information on cycloalkane conformation as it relates to sugar structure.